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PATENT SPECIFICATION

(11) 1238959

1238959

NO DRAWINGS

- (21) Application No. 55816/68 (22) Filed 25 Nov. 1968
 (31) Convention Application No. 687101 (32) Filed 1 Dec. 1967 in
 (33) United States of America (US)
 (45) Complete Specification published 14 July 1971
 (51) International Classification A 61 k 27/00
 (52) Index at acceptance

ASB 381 38Y 401 40Y 410 411 41Y 440 44Y 451 453
 45Y 462 463 46Y 471 472 47Y 480 482 483
 484 485 48Y 490 492 493 49Y 500 502 503 504
 505 50Y 510 511 513 51Y 522 526 52Y 531
 533 53Y 540 541 543 546 54Y 550 55Y 565 566
 56Y 576 57Y 586 58Y 616 61Y 640 641 64Y
 650 651 652 65X 65Y 660 661 663 664 666 667
 66Y 670 67Y
 C2C 173—197—288 17X—27X—287 1E4K4 1E6K4
 1E6K6 1E7E1 1E7F1 1E7G 1E7H2 1E7N5 1G5A
 1G5B 1G6A1 1G6B3 1G6B4 1K1A1 1K1C3
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 1Q7A 1Q8A 1Q8C 1Q9B 215 220 226 22Y 246
 250 251 25Y 30Y 313 31Y 321 322 323 326
 328 32Y 332 334 337 338 340 341 342 34Y 351
 352 364 36Y 373 37Y 385 3A10E3A4 3A10E5F1C
 3A10E5F2A 3A10E5J 3A12A4A 3A12B1 3A12B2
 3A12C3 3A12C4 3A12C6 3A13C10D 3A13C10H
 3A13C1C 3A13C2C 3A13C3C 3A13C6A 3A13C6C
 3A14A3A 3A14A5 3A14A7A 3A14A7C 3A14A8D
 3A14B3E 3A14B8D 3A16 3A8A4 3A8B1 3A8G1
 3A8G4 3C4 3C5A4 3C5C4 3C5C7 3C5E1 3C5E2
 3C6 43X 500 50Y 510 51X 536 537 538 574
 5A4 5E2 5E5 601 603 614 620 621 626 627
 62X 62Y 650 656 660 661 666 670 671 672 680
 681 682 699 69Y 708 720 72X 72Y 73Y 758
 761 762 790 79Y B4A2 B4B B4C B4E KA KD
 KS LF LK MD MG ML MM NR RM RV SF

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(54) ANTIINFLAMMATORY METHOD AND COMPOSITIONS

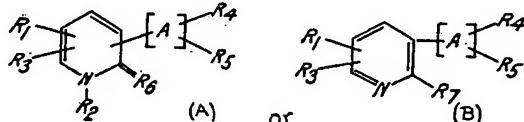
(71) We, MERCK & Co. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to the treatment of inflammation.

This invention provides a method of treating inflammation in non-human animals which comprises the administration to the animal of from 0.5 to 30 mg/kg of body weight/day of a compound having the formula:

10

10



in which

R₁ is hydrogen, alkyl, phenyl, aralkyl, halogen, haloalkyl, alkoxy, amino, dialkylamino, dialkylaminoalkyl, nitro, alkylsulfonyl, phenylsulfonyl, phenoxy, sulfo or triphenylmethyl;

[Price 25p]



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R₁ is hydrogen, alkyl, alkenyl, hydroxyl, amino, alkylbenzyl, substituted phenyl, quinolyl, aralkyl, aralkenyl, benzamido, C₁-alkyl, phenyl, phenyl-substituted amine, alkoxycarbonylamine, benzylideneamine, C₁-alkanoyl, phenyltricido, benzoxycarbonyl-alkyl, dialkylaminokally, (C₁-alkanoyl)-alkyl, carboxyalkyl, hydroxylalkyl, carboxy, alkyl, alkylaminokally, hydroxyl, mercapto, alkylthio, alkylsulfanyl, alkylsulfonyl, carbamoyl, dialkylsulfamoyl, hydroxyl, amino, dialkylamine, nitro, cyano, sulfamoyl, alkylsulfonyl, carbamoyl, substituted alkyl, hydroxyl, amino, dialkylamine, phenyltricido, benzoxycarbonyl, each of R₁ and R₂, which are the same or different, is hydrogen, alkyl, phenyl, R₁ is oxygen or sulfur; R₂ is OK, or SR₃. In the past, a standard treatment of inflammation has been to administer various compounds of the steroid class. These had the greater disadvantages of a fleeting effect and side reactions. It has now been found that dimethylamine can be treated advantageously with 3- or 4-phenyl-2-[1H]-pyridine having formula A or B above including the parent compound or 4-amino-2-[1H]-pyridine is diazotized in the presence of benzene. The reactions described operate equally for the 4-phenyl-pyridine (3 or 4-amino-2-[1H]-pyridine) and the 4-phenyl-pyridine (3 or 4-phenyl-2-[1H]-pyridine). The N-oxide is treated with chlorinating agent (3 or 4-phenyl-2-[1H]-pyridine). Alternatively, the N-oxide is treated with chlorine (3 or 4-phenyl-2-[1H]-pyridine). Alternatively, the N-oxide is converted by reaction with aqueous basic hydroxyls giving the 2-acetyl-3-phenylpyridine which upon acidification gives the 2-chloro-3-phenylpyridine. The 2-chloro-3-phenylpyridine also upon hydrolysis gives the 3- or 4-phenyl-2-[1H]-pyridine. The 2-chloro-3-phenylpyridine is also upon hydrolysis gives the 3- or 4-phenyl-2-[1H]-pyridine. The 2-chloro-3-phenylpyridine may be converted to the 3- or 4-phenyl-2-[1H]-pyridones by treatment with phosphorus pentasulfide. The 3- or 4-phenyl-2-[1H]-pyridones (Compound VI) in the Flow Sheer may be converted to the 3- or 4-phenyl-2-[1H]-pyridones (Compound VII) by the action of alkylating agents. Certain other compounds to be used in this method of alkylating agents. The 3- or 4-phenyl-2-[1H]-pyridones (Compound VI) in the Flow Sheer is also prepared by direct oxidation of the sodium alcoholate or thioalcoholate. When 3- or 4-(nitrophenyl)-pyridones are of the sodium alcoholate or thioalcoholate, the 2-chloropyridines may be used, by way of a Sandmeyer type of reaction, to prepare halo, cyanato or mercapto derivatives. It should be noted that the reactions shown in the Flow Sheer are numbered with pyridines at a benzene to get Compound VII, directly, nitro benzenes can be heated with pyridines to form the pyridone open chain substituent on a benzene compound can be cyclized to form the pyridone. Other methods have been known in the literature for the preparation of (3 or 4)-phenyl-2-[1H]-pyridones. A (3 or 4)-amino-2-phenylbenzopyridine can be diazotized in the presence of a benzene to get Compound VII, directly, nitro benzenes can be heated with pyridines at very elevated temperatures to produce (3 or 4)-phenylpyridines. An open chain substituent on a benzene compound can be cyclized to form the pyridone.

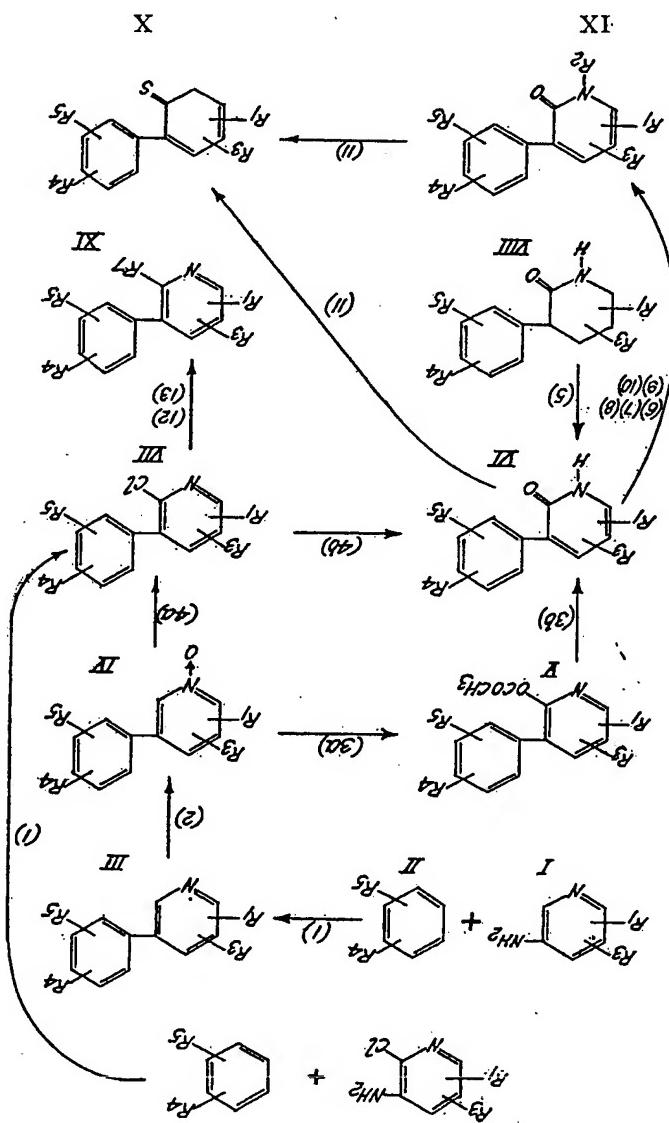
ring or a piperidone ring which can be oxidized as described above to the 3- or 4-phenyl-2[1H]-pyridone. A (3 or 4)-phenylpyridine 2-sulfonic acid, upon fusion with caustic, gives a 3- or 4-phenyl-2[1H]-pyridone. An alpha pyrone can be treated with ammonia to give a 3- or 4-phenyl-2[1H]-pyridone. 3- or 4-phenylpyridines can be hydroxylated directly in the vapor phase. 3- or 4-phenyl 2-aminopyridines can be diazotized and the diazo compound hydrolysed to give a 3- or 4-phenyl-2[1H]-pyridone. The N-oxides (Compound IV) can be rearranged under the influence of light to give the 3-phenyl-2-[1H]-pyridones. The 1-substituted-3- or 4-phenyl-2[1H]-pyridones (Compound IX) can be prepared by the direct oxidation of the corresponding 3- or 4-phenyl N-pyridinium compounds. These various preparations generally are not as practical in the synthesis of these compounds as the ones described in the Flow Sheet, being either highly selective and applicable to only a few compounds, giving poorer yields or having other inherent weaknesses.

In the treatment of inflammation by 3-phenyl-2[1H]-pyridones, the medicament may be administered orally, intravenously or applied topically. The invention provides pharmaceutical compositions comprising a compound of formula A or B above together with a solid inert diluent, carrier or coating, a flavoured liquid carrier or diluent, or an isotonic injectable liquid carrier or diluent. Also in accordance with the present invention, compounds of formula A or B made by the processes of the present invention are incorporated in pharmaceutical or veterinary compositions that also comprise an inert diluent, carrier or coating. In formulations, it can be pressed into shaped dosage forms, such as pills or tablets, or be encapsulated or dissolved in isotonic solution for I.V. use or made into ointments for topical use. The standard pharmaceutical ingredients normally used in such pharmaceutical formulations can be used in formulating these compounds. Inflammation is treated by the administration of from 0.5 to 30 milligrams of the compound per kg body weight per day. An example of the above class is the simple unsubstituted 3-phenyl-2[1H]-pyridone which should be administered in a dosage range of from 2 to 15 mg/kg of body weight/day. The 3-phenyl-2[1H]-pyridone is effective at 10—30 milligrams per kilogram in rats. The compositions of the present invention may be applied to either animal or human patients since all warm-blooded species are subject to the ills of inflammation.

FLOW-SHEET

02

Reactions



8. Reaction with a strong base such as NaH in an inert atmosphere, followed by heating with iodobenzene or a substituted iodobenzene.
9. Stirring at low temperatures, preferably cold with an N-halo amino compound.
10. Heating with an alkanic acid anhydride, preferably with acetic anhydride at 130—140°C.
- 5 11. Heating with P_2S_5 (in the absence of OH, ketone or amino groups in the molecule).
12. Heating with a metal alkoxide or other alcoholate.
13. Heating with a metal mercaptide.
- 10 The preparation of compounds used in the method and compositions of this invention is illustrated by the following Examples 1—34 and some test results are set forth in Example 35.

EXAMPLE 1

15 A. 3-Aminopyridine (39 g.) in 1.5 l. of anhydrous benzene is treated with amyl nitrite (68 g.) and the resulting mixture heated slowly to 81°C., and kept overnight at this temperature. The solution is decanted from some tar which has precipitated, and the excess benzene removed *in vacuo*. Distillation of the residue yields 3-phenylpyridine (38 g.; 59%), b.p. 102—105.5° (2.5 mm.) as a yellow oil.

20 Similarly, when 4-amino pyridine is used in the above example in place of 3-amino pyridine, there is obtained 4-phenylpyridine.

25 B. Similarly, when the benzene in Part 1A is replaced by toluene, anisole, benzonitrile, nitrobenzene, fluorobenzene, benzotrifluoride, naphthalene, *o*-, *m*-, and *p*-xylenes, *o*-, *m*- and *p*-dichlorobenzenes, hydroquinone dimethyl ether, veratrole, resorcinol dimethyl ether, biphenyl, thiophene, furan or thiazole, the corresponding substituted phenylpyridines, 3-(*o*-, *m*-, and *p*-methylphenyl)-pyridines, 3-(*o*-, *m*-, and *p*-methoxyphenyl)-pyridines, 3-(*o*-, *m*-, and *p*-cyanophenyl)-pyridines, 3-(*o*-, *m*- and *p*-nitrophenyl)-pyridines, 3-(*o*-, *m*- and *p*-fluorophenyl)-pyridines, 3-(*o*-, *m*-, and *p*-trifluoromethylphenyl)-pyridines, 3-(α - and β -naphthyl)-pyridines, 3-(*o*,*m*-, *m*,*p*, *o*,*o*'-*o*,*p*-, *m*,*m*' and *o*,*m*' dimethylphenyl)-pyridines, 3-(*o*,*m*-, *m*,*p*-, *o*,*o*'-, *o*,*p*-, *m*,*m*'-, and *o*,*m*'-dichlorophenyl)-pyridines, 3-(*o*,*m*-, *m*,*p*-, *o*,*o*'-, *o*,*p*-, *m*,*m*'- and *o*,*m*'-dimethoxyphenyl)-pyridines, 3-(*o*-, *m*-, and *p*-biphenyl)-pyridines, 3-(2-thienyl)-pyridines, 3-(2'- and 3'-furyl)-pyridines, and 3-(2', 4'- and 5'-thiazolyl)-pyridines are obtained after separation of isomers via fractional distillation and/or column and vapor-phase chromatography.

35 C. 3-Aminopyridine (39 g.) in 1.5 l. of anhydrous chlorobenzene is treated with amyl nitrite (68 g.) as described in (A) above. Distillation of the concentrated reaction mixture yields 35.4 g. of the three isomers, b.p. 110—130° at ca. 2.5 mm. The fraction boiling 110—113° at ca. 2.5 mm. consists of 11.5 g. of nearly one component material; I.R., N.M.R., U.V. and T.L.C. on this and on products derived from this indicate the *o*-isomer. The other isomers are isolated from the higher boiling fractions via purification of their picrates, followed by regeneration of the free bases. When 4-aminopyridine is used in place of 3-aminopyridine in the above procedure, the corresponding 4-phenylpyridines are obtained.

40 D. In cases where the benzene-substitute is a solid, an inert co-solvent is used and the amount of benzene-substitute reduced. Also, the phenylpyridines listed in (A) above are obtained by coupling a substituted aniline, as *o*-chloroaniline, with pyridine via the above procedure, and separating the isomeric α -, β - and γ -pyridines, to give the desired 3-(substituted phenyl)-pyridine.

45 E. When 5-amino-2-picoline is used in place of 3-aminopyridine in procedure (A) above, 6-methyl-3-phenyl-pyridine is obtained. Similarly, when 5-amino-3-picoline, 3-amino-4-picoline, 5-amino-2-chloropyridine, 3-amino-5-chloropyridine, 3-amino-4-chloropyridine, 5-amino-2-methoxypyridine, 3-amino-5-methoxypyridine, 3-amino-4-methoxypyridine, 5-amino-2-nitropyridine, 3-amino-5-nitropyridine, 3-amino-4-nitropyridine, 5-amino-2-ethoxypyridine, 3-amino-5-ethoxypyridine, 3-amino-4-ethoxypyridine, 5-amino-2-ethylpyridine, 3-amino-4-ethylpyridine, 5-amino-2-phenethylpyridine, 3-amino-4-phenethylpyridine, 5-amino-2-fluoropyridine, 5-amino-2-(methylsulfonyl)-pyridine, 3-amino-4-(methylsulfonyl)-pyridine, 5-amino-2-(phenylsulfonyl)-pyridine, 5-amino-3-chloro-2-phenoxy-pyridine, 5-amino-2-methoxy-4-picoline, and 3-amino-5-phenyl-4-picoline are used in place of 3-aminopyridine in the same procedure, 5-methyl-3-phenylpyridine, 4-methyl-3-phenylpyridine, 6-chloro-3-phenylpyridine, 5-chloro-3-phenylpyridine, 4-chloro-3-phenylpyridine, 6-methoxy-3-phenylpyridine, 5-methoxy-3-phenylpyridine, 4-methoxy-3-phenylpyridine, 6-nitro-3-phenylpyridine, 5-nitro-3-phenylpyridine, 4-nitro-3-phenylpyridine, 6-ethoxy-3-phenyl-

A. 3-Phenylpyridine-N-oxide (9.2 g.) and 25 ml. of acetic anhydride are heated in an oil-bath to 153°C. (bath temperature), under a nitrogen atmosphere, the stirred mixture kept elevated for three hours at this temperature, the stirred mixture cooled to room temperature, and the dark mixture added slowly to a stirred ice-water mixture (250 ml.) covered with ca. 50 ml. of ether. After solidification of the oily mixture occurs, the solid is collected, washed well with water and ether, and dried to give 7.7 g. of tan, nearly

EXAMPLE 3

A. 3-*o*-Chlorophenylpyridine (11.4 g.) in 40 ml. of glacial acetic acid is treated at 27°C. with 7 ml. of 30% hydrogen peroxide solution. The mixture is heated gently, in this case 75 ± 20 ° is preferred and kept overnight, during which time another 9 ml. of hydrogen peroxide is added in 6 cc. and 3 ml. portions. After cooling, solid sodium bisulfite is added in small portions as needed to destroy the excess peroxide, the mixture is concentrated to ca. one-half the volume, 75 ml. of water is added, the mixture concentrated to ca. one-half the volume, 75 ml. of water is added, the mixture concentrated to ca. 250 ml. The white solid chloroplatinates is filtered, washed with ether and dried to give 8.4 g. 3-*o*-chlorophenylpyridine-N-oxide, m.p. 118°-123°, I.R. 8.26 μ . This material is used without further purification.

EXAMPLE 2

(E) which the unsubstituted benzenees of (b) are used in place of benzenee in part (F); when the unsubstituted benzenees of (b) are used in place of benzenee in part (E) above, the corresponding phenyl-substituted phenyl-substituted pyridines are obtained.

pure solid. Recrystallization from dimethylsulfoxide followed by recrystallization from chloroform and treatment with decolorizing charcoal yields white crystals, m.p. 225—227°C., of 3-phenyl-2-[1H]-pyridone.

B. 3-(*o*-Chlorophenyl)-pyridine-*N*-oxide (4.1 g.) and acetic anhydride (10 ml.) are heated, under nitrogen, in an oil bath to 146±2° (bath temperature) and maintained on this temperature for *ca.* eleven hours. On cooling, the mixture is added to a stirred ice-water mixture (80 ml.), and the resultant oil taken up in chloroform. The chloroform is removed *in vacuo*, the residue dissolved in 60 ml. methanol, 7 ml. water and 2 ml. saturated aqueous sodium bicarbonate added, the mixture refluxed *ca.* 15 minutes, the mixture made neutral with 2.5 N hydrochloric acid, the solvents removed, and the residue partitioned between chloroform-water. The chloroform layer is dried, stripped of solvent, and the residue recrystallized from benzene to yield 635 mg. white 3-(*o*-chlorophenyl)-2-[1H]-pyridone, m.p. 203.5—207°.

C. Alternately, the acetic anhydride may be stripped *in vacuo* directly and the methanol-bicarbonate treatment used immediately.

D. When the substituted pyridine oxides from Example 2 are used in place of 3-(*o*-chlorophenyl)-pyridine oxide in the above reaction, the corresponding 2-[1H]-pyridones:

3-(*o*-, *m*- and *p*-methylphenyl)-2-[1H]-pyridones,
3-(*m*- and *p*-chlorophenyl)-2-[1H]-pyridones,
3-(*o*-, *m*- and *p*-methoxyphenyl)-2-[1H]-pyridones,
3-(*o*-, *m*- and *p*-cyanophenyl)-2-[1H]-pyridones
3-(*o*-, *m*- and *p*-nitrophenyl)-2-[1H]-pyridones,
3-(*o*-, *m*- and *p*-fluorophenyl)-2-[1H]-pyridones,

3-(*o*-, *m*- and *p*-trifluoromethylphenyl)-2-[1H]-pyridones,

3- α - and β -naphthyl-2-[1H]-pyridones,

3-(*o*,*m*-dimethylphenyl)-2-[1H]-pyridone,

3-(*m*,*p*-dimethylphenyl)-2-[1H]-pyridone,

3-(*o*,*o'*-dimethylphenyl)-2-[1H]-pyridone,

3-*o*,*p*-dimethylphenyl)-2-[1H]-pyridone,

3-(*m*,*m'*-dimethylphenyl)-2-[1H]-pyridone,

3-(*o*,*m'*-dimethylphenyl)-2-[1H]-pyridone,

the corresponding dichloro and dimethoxy phenyl pyridones,

3-(*o*-, *m*- and *p*-biphenylyl)-2-[1H]-pyridones,

3-(2'-thienyl)-2-[1H]-pyridone,

3-(2'-furyl)-2-[1H]-pyridone,

3-(2'-thiazolyl)-2-[1H]-pyridone,

3-(4'-thiazolyl)-2-[1H]-pyridone,

3-(5'-thiazolyl)-2-[1H]-pyridone,

6-methyl-3-phenyl-2-[1H]-pyridone,

5-methyl-3-phenyl-2-[1H]-pyridone,

4-methyl-3-phenyl-2-[1H]-pyridone,

6,5- and 4-chloro-3-phenyl-2-[1H]-pyridones,

6,5- and 4-methoxy-3-phenyl-2-[1H]-pyridones,

6,5- and 4-nitro-3-phenyl-2-[1H]-pyridones,

6,5- and 4-ethoxy-3-phenyl-2-[1H]-pyridones,

6- and 4-ethyl-3-phenyl-2-[1H]-pyridones,

6- and 4-phenethyl-3-phenyl-2-[1H]-pyridones,

6-fluoro-3-phenyl-2-[1H]-pyridone,

6- and 4-methylsulfonyl-3-phenyl-2-[1H]-pyridones,

6-phenylsulfonyl-3-phenyl-2-[1H]-pyridone,

5-chloro-6-phenoxy-3-phenyl-2-[1H]-pyridone,

6-methoxy-4-methyl-3-phenyl-2-[1H]-pyridone,

4-methyl-3,5-diphenyl-2-[1H]-pyridone,

and the corresponding 3-substituted-phenyl derivatives of the above compounds are obtained.

E. In the above cases, the inductive effects of the substituents on the phenyl and pyridine rings help determine the course of the rearrangement, and in some cases of the corresponding 5-phenyl-2-[1H]-pyridones are obtained. The isomers are separated by recrystallization and column chromatography techniques.

EXAMPLE 4

A. 2-Methyl-5-phenylpyridine-*N*-oxide (1 g.), phosphorus pentachloride (1.2 g.) and dry chloroform (10 ml.) are refluxed on the water-bath for 1 hour. Ice is added to

EXAMPLE 8

A. *Sodium 3-phenyl-pyridone*

To a suspension of 0.87 gram of 50% NaH (0.018 m.) in 100 mls. of dry benzene is added 3.08 grams (0.018 m.) of 3-phenyl-2[1H]-pyridone. The reaction mixture is heated at 35°C. for 6 hours and allowed to stir at room temperature overnight. The benzene was then evaporated *in vacuo* leaving a residue of sodium 3-phenyl-pyridone.

B. *1,3-Diphenyl-2[1H]-pyridone*

The sodium 3-phenyl-pyridone from above (0.018 m.), 6.04 grams of iodo benzene (0.032 m.) and 0.19 grams of copper (0.003 m.) are mixed with mechanical stirring and heated at 155° under nitrogen for six hours. The reaction mixture is allowed to cool to room temperature overnight and the mixture then extracted well with chloroform. The chloroform extracts are washed with water, dried over sodium sulfate and concentrated. Chromatography of the residue on 500 grams of silica gel and elution with ether-petroleum ether (0—75%) gives 1,3-diphenyl-2[1H]-pyridone.

C. Similarly, when substituted iodo benzenes, e.g. 2-iodonitrobenzene, 3-iodonitrobenzene and 4-iodonitrobenzene, are used in place of iodo benzene in the above example, the corresponding 1-(substituted aryl)-3-phenyl-2[1H]-pyridones are obtained.

EXAMPLE 9

3-Phenyl-1-(2'-quinolyl)-2[1H]-pyridone

A. *2-Bromo-3-phenyl-pyridine*

A mixture of 0.1 moles of 3-phenyl-2[1H]-pyridone and 0.15 moles of phosphorus tribromide are heated for 3 hours at 180°. The reaction mixture is cooled, decomposed in ice water, made alkaline with sodium hydroxide and extracted well with ether. The combined ethereal extracts are dried over sodium sulfate and concentrated *in vacuo* to yield 2-bromo-3-phenyl-pyridine.

B. *3-Phenyl-1(2'-quinolyl)-2[1H]-pyridone*

A mixture of 0.02 mole of quinoline-N-oxide and 0.022 mole of 2-bromo-3-phenyl-pyridine is heated on the steam bath for 8 hours. The reaction mixture is cooled, taken up in water containing a little hydrochloric acid and washed with ether. The aqueous layer is made alkaline with potassium carbonate solution and extracted well with chloroform. The combined chloroform extracts are dried over potassium carbonate and concentrated to yield 3-phenyl-1-(2'-quinolyl)-2[1H]-pyridone.

C. Similarly, when 2-picoline-N-oxide, 3-picoline-N-oxide or 4-picoline-N-oxide is used in place of quinoline-N-oxide in the above procedure, there is obtained 3-phenyl-1-[2'-(6'-methylpyridyl)]-2[1H]-pyridone, 3-phenyl-1-[2'-(5'-methylpyridyl)]-2[1H]-pyridone, and 3-phenyl-1-[2'-(4'-methylpyridyl)]-2[1H]-pyridone.

EXAMPLE 10

A solution of chloramine is prepared by treating at 0°C. 65 ml. of a 1.93 m. neutral sodium hypochlorite solution (0.125 m.) with 20 mls. of 1.84 m. NH₂OH (0.375 m.). The above mixture is allowed to stand for one hour in an ice-salt bath and then 0.125 m. of sodium 3-phenyl-pyridone is added. The reaction mixture is stirred overnight at 0—10°C. and is then continuously extracted with ether for 24 hours. The ethereal extracts are dried over sodium sulfate and concentrated to yield 1-amino-3-phenyl-2[1H]-pyridone.

EXAMPLE 11

1-Hydroxy-3-phenyl-2[1H]-pyridone

A. *2-Chloro-3-phenyl-pyridine-N-oxide*

0.2 mole of 2-chloro-3-phenyl-pyridine is treated with 25 mls. of glacial acetic acid and 22 mls. of 40% peracetic acid. The temperature of the reaction mixture is kept at 70°C. for 3 hours. The reaction mixture is concentrated and extracted with chloroform and the chloroform extracts are concentrated to yield 2-chloro-3-phenyl-pyridine-N-oxide.

B. 0.01 mole of 2-chloro-3-phenyl-pyridine-N-oxide and 20 mls. of acetic anhydride are heated for 3 hours at 130—140°. The reaction mixture is then concentrated *in vacuo* to yield crude 1-hydroxy-3-phenyl-2[1H]-pyridone.

EXAMPLE 12

A. A mixture of 0.02 mole of 3-phenyl-2[1H]-pyridone and 0.025 mole of phosphorus pentasulfide is heated for 6 hours at 160°C. The reaction mixture is then

3-Phenyl-2-[1H]-pyridone (3.08 g.) and N-chlorosuccinimide (2.7 g.) are refluxed in methylene chloride (25 ml.) for 28 hours under a nitrogen atmosphere. The mixture is filtered with ca. 20 more ml. OH^- washed with water ($2 \times$ ca. 50 ml.), dried over magnesium sulfate, filtered, concentrated to 3.2 g., then solid. Recrystalliza-

EXAMPLE 17

The following examples illustrate the interconversion or introduction of functional groups after preparation of the phenyl pyridine nucleus.

A mixture of 0.01 mole of $\text{I}-(2\text{-hydroxyethyl})-3\text{-phenyl}-2\text{[IH]-pyridone}$ and 25 cc. of concentrated hydrochloric acid is heated in a sealed tube for 60 hours at 120°. The reaction mixture is cooled and then concentrated in *vacuo* to yield $\text{I}-(2\text{-chloroethyl})-3\text{-phenyl}-2\text{[IH]-pyridone}$.

EXAMPLE 16

A mixture of 0.01 mole of 1-(2-*o*-anisidinyl)-3-phenyl-2-[1H]-pyridine, 50 ml. of acetic acid and 50 ml. of 10% sulfuric acid is refluxed for 4 hours. The reaction mixture is then concentrated, poured into water and extracted well with chloroform. The combined chloroform extracts are dried over sodium sulfate and concentrated to give 1-(2-carboxyethyl)-3-phenyl-2-[1H]-pyridine.

EXAMPLE 14

B. Similarly, when the other substituted 2-chloro-3-phenyl-pyridines are used in place of 2 - chloro - 3 - phenyl - pyridine, the corresponding 2 - methoxyphenoxypyridines are obtained. When other alkoxides such as sodium phenoxypyridines are prepared, sodium phenolate, sodium - o - or p - chlorophenolate or propoxide, sodium phenoxy, sodium phenoate, sodium phenoxide, or methoxyphenoxide, sodium benzoate, or methoxybenzoate, sodium chloroformate, or methanol, such as in the above examples, the corresponding alkoxypropyridines are obtained.

Uranium sulfate

A mixture of 0.01 mole of 2-chloro-3-phenylpyridine, 0.01 mole of sodium methoxide and 50 cc. of dry dimethylformamide is heated at 60° for 2 hours. The reaction mixture is cooled and washed with ether. The ether solution is extracted with 1N hydrochloric acid and the aqueous layer is extracted with ether. The ether solution is dried over calcium sulfate and the ether removed. The residue is recrystallized from benzene and dried. Yield: 2.29–2.37 g.

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tion from benzene (concentrating to *ca.* 40 ml. hot) yields 815 mg. very pale pink cotton-like crystals, m.p. 157.5—159°, of 5-chloro-3-phenyl-2[1*H*]-pyridone.

EXAMPLE 18

5-Dimethylamino-3-phenyl-2[1*H*]-pyridone

5-Chloro-3-phenyl-2[1*H*]-pyridone (1 g.) in anhydrous dimethylformamide (50 ml.) is saturated with dimethylamine, and the resultant mixture heated in a lined stainless-steel bomb for several hours. The solvent is removed *in vacuo*, the residue distributed between chloroform and water, the chloroform layer dried, solvent stripped, and the residue chromatographed on a silica gel column using a methanol-methylene chloride eluent ('/v0—100% MeOH) to yield the title compound.

EXAMPLE 19

3-*p*-Hydroxyphenyl-2[1*H*]-pyridone

3-(*p*-Methoxyphenyl)-2[1*H*]-pyridone (2 g.) is added to a stirred 10-g. portion of pyridine hydrochloride at 188°. A dry nitrogen atmosphere is maintained. The mixture is kept 20 minutes, allowed to cool, then added to 45 g. of ice. The crude product is collected, dried and recrystallized to yield the title compound.

Similarly, when the *o*- and *m*-methoxyphenylpyridones are substituted for the *p*-isomer in the above reaction, the corresponding *o*- and *m*-hydroxy analogs are obtained.

EXAMPLE 20

3-(*p*-Aminophenyl)-2[1*H*]-pyridone

3-(*p*-Nitrophenyl)-2[1*H*]-pyridone (1 g.) in warm dioxane (50 ml.) is reduced under a hydrogen atmosphere in the presence of 0.3 g. 5% Pd/C. The mixture is filtered, the cake washed well with warm dioxane, the combined filtrates concentrated to residue, the residue recrystallized to yield title compound.

Alternatively, when the dioxane solution is treated with anhydrous ethereal-hydrogen chloride solution, the hydrochloride precipitates. When the corresponding *o*- and *m*-nitrophenyl-pyridones are used in the above reduction the *o*- and *m*-aminophenyl-pyridones are obtained.

EXAMPLE 21

3-(*p*-Dimethylaminophenyl)-2[1*H*]-pyridone

3-(*p*-Nitrophenyl)-2[1*H*]-pyridone (1 g.) in methanol (100 ml.) containing glacial acetic acid (1 ml.) and 37% formaldehyde solution (3 ml.) is reduced in the presence of Raney nickel (1/4 tsp.) under a hydrogen atmosphere. The mixture is filtered, the cake washed with methanol, and the combined filtrates concentrated to a residue. Chromatography on an alumina column using a system comprising methanol and methylene chloride ('/v0—100%) yields the title compound.

When the *o*- and *m*-nitro isomers are used in place of the *p*-isomer in the above reduction, the corresponding *o*- and *m*-dimethylaminophenyl-2-pyridones are obtained.

EXAMPLE 22

3-(*p*-Carbamoylphenyl)-2[1*H*]-pyridone

3-(*p*-Cyanophenyl)-2[1*H*]-pyridone (5 g.) is added to a stirred ice-cold portion of concentrated sulfuric acid (20 g.) and the mixture stirred overnight, added to ice-water, the crude product collected, dried and recrystallized to yield the title compound. When the *o*- and *m*-cyanophenylpyridones are used in the above reaction, the corresponding *o*- and *m*-carbamoylphenyl isomers are obtained.

EXAMPLE 23

3-(*p*-Carboxyphenyl)-2[1*H*]-pyridone

3-(*p*-Cyanophenyl)-2[1*H*]-pyridone (1 g.) in 30 ml. of a 1:1 mixture of glacial acetic acid and 20% hydrochloric acid is heated for twelve hours, the solvent removed *in vacuo*, the residue partitioned between chloroform and nearly saturated sodium bicarbonate solution, the bicarbonate solution filtered and acidified, the precipitate collected, dried and recrystallized to yield the title compound.

When the *o*- and *m*-cyanophenyl-pyridones are used in the above reaction, the corresponding *o*- and *m*-carboxyphenyl isomers are obtained.

EXAMPLE 24

1-Methyl-3-phenyl-2[1*H*]-pyridone-5-sulfonic acid

When 1-methyl-3-phenyl-2[1*H*]-pyridone is treated with chlorosulfonic acid according to the procedure of German Patent 601,896, there is obtained 1-methyl-3-phenyl-2[1*H*]-pyridone-5-sulfonic acid.

5	Example 25 3-Phenyl-5-triphenylmethyl-2-[1H]-pyridone When 3-nitro-5-triphenylmethyl-2-[1H]-pyridone is reduced under the conditions described in Example 20 above, the title compound is obtained.	the corresponding 4- and 6-nitro isomers are used in place of the 5-nitro compound, and 60 ml. of boiling ethanol added, the solid filtered, washed with fresh ethanol, and recrystallized to give the title compound.
10	Example 26 5-Amino-3-phenyl-2-[1H]-pyridone When 5-nitro-3-phenyl-2-[1H]-pyridone is reduced under the conditions described in Example 20 above, the title compound is obtained.	the corresponding 4- and 6-nitro isomers are used in place of the 5-nitro compound, and 60 ml. of boiling ethanol added, the solid filtered, washed with fresh ethanol, and heated at ca. 250° in a metal-bath for 30 minutes, the reaction mixture cooled, and recrystallized to give the title compound.
15	Example 27 5-Methyl-3-phenyl-2-[1H]-pyridone 5-Dimethylaminomethyl-3-phenyl-2-[1H]-pyridone In carbon tetrachloride (250 ml.) are reduced under irradiation for ca. 15 mins. (occasionally a trace of benzoyl peroxide is necessary to initiate reaction), cooled, filtered, and the filtrate concentrated in vacuo to a residue.	The residue is taken up in dimethylformamide, dimethylaminomethylamine added, the vessel sealed and heated, the solvent removed in vacuo, and the residue chromatographed on an alumina column using a methanol-methylene chloride system (v/v 0—100%) as eluent to yield the title compound.
20	Example 28 3-(p-Mercaptophenyl)-2-[1H]-pyridone The title compound is prepared from 3-(p-aminophenyl)-2-[1H]-pyridone by the procedure of Table II & Fukushima for thioether (Org. Syn., Vol. III, p. 809).	Similarly, when the 4- and 6-mercapto isomers are used in place of the p-isomer in an alumina column using a methanol-methylene chloride system (v/v 0—100%) as eluent to yield the title compound.
25	Example 29 3-(p-Mercaptophenyl)-2-[1H]-pyridone The procedure used by Wallace (Tetrahedron Letters (1963) 1131) for benzene sulfonic acid is used.	the corresponding 4- and 6-mercapto isomers are used in place of the p-isomer in an alumina column using a methanol-methylene chloride system (v/v 0—100%) as eluent to yield the title compound.
30	Example 30 p-(2-[1H]-Pyridin-3-yl)-benzenesulfonic acid p-(2-[1H]-Pyridin-3-yl)-benzenesulfonamide The procedure is stirred at room temperature in vacuo, dry benzene (50 ml.) containing one drop of dimethylformamide. The mixture is stirred over-night at room temperature, the excess of thionyl chloride removed in vacuo, dry benzene added, removed in vacuo, and the residue purified out to remove all traces of thionyl chloride. The acid chloride is then taken up in anhydrous ether and added to an aqueous solution containing two equivalents of ammonia, stirred for several hours, the product collected, dried and treated as in Example 4B above to hydrolyze any 2-chloro derivative present. Recrystallization yields p-(2-[1H]-pyridin-3-yl)-benzenesulfonamide.	Similarly, when the 4- and 6-mercapto isomers are used in place of the p-isomer in an aqueous solution containing two equivalents of ammonia, stirred for several hours, the residue is taken up in anhydrous ether and added to an aqueous solution containing thionyl chloride. The acid chloride is then taken up in anhydrous ether and added to an aqueous solution containing two equivalents of ammonia, stirred for several hours, the product collected, dried and treated as in Example 4B above to hydrolyze any 2-chloro derivative present. Recrystallization yields p-(2-[1H]-pyridin-3-yl)-benzenesulfonamide.
35	Example 31 p-(2-[1H]-Pyridin-3-yl)-benzenesulfonic acid p-(2-[1H]-Pyridin-3-yl)-benzenesulfonamide The procedure used by Wallace (Tetrahedron Letters (1963) 1131) for benzene sulfonic acid is used.	the corresponding 4- and 6-mercapto isomers are used in place of the p-isomer in an aqueous solution containing two equivalents of ammonia, stirred for several hours, the residue is taken up in anhydrous ether and added to an aqueous solution containing thionyl chloride. The acid chloride is then taken up in anhydrous ether and added to an aqueous solution containing two equivalents of ammonia, stirred for several hours, the product collected, dried and treated as in Example 4B above to hydrolyze any 2-chloro derivative present. Recrystallization yields p-(2-[1H]-pyridin-3-yl)-benzenesulfonamide.
40	Example 32 3-(p-Mercaptophenyl)-2-[1H]-pyridone The procedure is stirred at room temperature in vacuo, dry benzene (50 ml.) containing one drop of dimethylformamide. The mixture is stirred over-night at room temperature in vacuo, dry benzene added, removed in vacuo, and the residue purified out to remove all traces of thionyl chloride. The acid chloride is then taken up in anhydrous ether and added to an aqueous solution containing two equivalents of ammonia, stirred for several hours, the product collected, dried and treated as in Example 4B above to hydrolyze any 2-chloro derivative present. Recrystallization yields p-(2-[1H]-pyridin-3-yl)-benzenesulfonamide.	the corresponding 4- and 6-mercapto isomers are used in place of the p-isomer in an aqueous solution containing two equivalents of ammonia, stirred for several hours, the residue is taken up in anhydrous ether and added to an aqueous solution containing two equivalents of ammonia, stirred for several hours, the product collected, dried and treated as in Example 4B above to hydrolyze any 2-chloro derivative present. Recrystallization yields p-(2-[1H]-pyridin-3-yl)-benzenesulfonamide.
45	Example 33 p-(2-[1H]-Pyridin-3-yl)-benzenesulfonamide ExAMPLE 30 When the o- and m-sulfonic acid isomers are used in the above reaction, the corresponding o- and m-sulfonic acids are obtained.	the corresponding 4- and 6-sulfonic acid isomers are used in place of the p-isomer in an aqueous solution containing two equivalents of ammonia, stirred for several hours, the residue is taken up in anhydrous ether and added to an aqueous solution containing two equivalents of ammonia, stirred for several hours, the product collected, dried and treated as in Example 4B above to hydrolyze any 2-chloro derivative present. Recrystallization yields p-(2-[1H]-pyridin-3-yl)-benzenesulfonamide.
50	Example 34 p-(2-[1H]-Pyridin-3-yl)-benzenesulfonic acid (0.005 M) is added to thionyl chloride (50 ml.) containing one drop of dimethylformamide. The mixture is stirred over-night at room temperature in vacuo, dry benzene added, removed in vacuo, and the residue purified out to remove all traces of thionyl chloride. The acid chloride is then taken up in anhydrous ether and added to an aqueous solution containing two equivalents of ammonia, stirred for several hours, the product collected, dried and treated as in Example 4B above to hydrolyze any 2-chloro derivative present. Recrystallization yields p-(2-[1H]-pyridin-3-yl)-benzenesulfonamide.	the corresponding 4- and 6-sulfonic acid isomers are used in place of the p-isomer in an aqueous solution containing two equivalents of ammonia, stirred for several hours, the residue is taken up in anhydrous ether and added to an aqueous solution containing two equivalents of ammonia, stirred for several hours, the product collected, dried and treated as in Example 4B above to hydrolyze any 2-chloro derivative present. Recrystallization yields p-(2-[1H]-pyridin-3-yl)-benzenesulfonamide.
55	Example 35 When the o- and m-sulfonamides are obtained.	When methylamine, dimethylamine or amiline is used in place of ammonia in the above reaction, the corresponding N-substituted sulfonamides are obtained.

EXAMPLE 31

2-Acetoxy-3-phenyl-pyridine

A mixture of 0.01 mole of 3-phenyl-pyridine-N-oxide is refluxed for 12 hours in 50 cc. of acetic anhydride. Concentration of the reaction mixture *in vacuo* yields 2-acetoxy-3-phenyl-pyridine.

EXAMPLE 32

1-Benzamido-3-phenyl-2[1H]-pyridone

A. To a mixture of 0.01 mole of 1-amino-3-phenyl-2-[1H]-pyridone and 5.0 grams of anhydrous potassium carbonate in 100 mls. of chloroform is added portionwise with stirring 0.01 mole of benzoyl chloride. The reaction mixture is stirred for 4 hours at reflux, then cooled and filtered. The filtrate is concentrated *in vacuo* to yield 1-benzamido-3-phenyl-2[1H]-pyridone.

B. When acetyl chloride is used in place of benzoyl chloride in the above example, there is obtained 1-acetamido-3-phenyl-2-[1H]-pyridone.

C. When carbobenzoxy chloride is used in place of benzoyl chloride in the procedure of part (A), 1-carbobenzoxyamino-3-phenyl-2[1H]-pyridone is obtained.

D. When ethyl chloroformate is used in place of benzoyl chloride in the procedure of part (A), 1-carbethoxyamino-3-phenyl-2[1H]-pyridone is obtained.

E. A mixture of 0.01 mole of 1-amino-3-phenyl-2[1H]-pyridone and 0.01 mole of benzaldehyde is refluxed for 3 hours in 30 mls. of ethanol. The reaction mixture is then concentrated to yield 1-benzylidineamino-3-phenyl-2[2H]-pyridone.

F. To 0.01 mole of 1-amino-3-phenyl-2[1H]-pyridone in 100 mls. of anhydrous ether is added 0.01 mole of phenylisocyanate. The reaction mixture is refluxed for one hour, then concentrated to yield 1-(*N'*-phenylureido)-3-phenyl-2[1H]-pyridone.

EXAMPLE 33

3-(*p*-Methylsulfinylphenyl)-2[1H]-pyridone

3-(*p*-Methylmercaptophenyl)-2[1H]-pyridone (0.001 mole) is stirred in methanol (50 ml.) and sodium metaperiodate (0.001 mole), dissolved in a minimum of water, is added. The mixture is stirred at room temperature for several days and then filtered. The filtrate is concentrated *in vacuo* and partitioned between chloroform and water. The chloroform layer is dried over sodium sulfate and the chloroform is removed *in vacuo*. The residue is recrystallized to yield the above compound.

When the *o*- and *m*-methylmercaptophenyl-pyridones are used in the above process, the corresponding *o*- and *m*-methylsulfinylphenyl-pyridones are obtained.

EXAMPLE 34

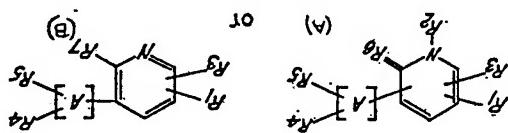
3-(*p*-Methylsulfonylphenyl)-2[1H]-pyridone

To 3-(*p*-Methylmercaptophenyl)-2[1H]-pyridone (1 g.) in glacial acetic acid (25 ml.) is added 30% aqueous hydrogen peroxide (2 ml.), and the resultant mixture is allowed to stir several days at room temperature. A minimum of sodium bisulfite is added to destroy the excess peroxide. The solvent is removed *in vacuo* and the residue is recrystallized to give the above compound.

When the *o*- and *m*-methylmercaptophenyl-pyridones are used in the above process, the corresponding *o*- and *m*-methylsulfonylphenyl-2[1H]-pyridones are obtained.

EXAMPLE 35

The testing procedures used are essentially those of 1) Winter, *et al*, Proc. Soc. Exper. Biol. 111 (1962), p. 544 (Carrogeenan-induced Foot Inflammation); 2) Stoerk *et al*, Am. J. Pathol. 30 (1954), p. 616 (Adjuvant Arthritis I); and 3) Newbould, Brit. J. Pharmacol. 24 (1965), p. 632 (Adjuvant Arthritis-II).



having the formula:

1. A method of treating inflammation in non-human animals that comprises administering to the animal from 0.5 to 30 mg/kg body weight/day of a compound

—WHAT WE CLAIM IS:—

Compound	Dose %	Inhibition %	Dose %	Inhibition %	Dose %	Inhibition %
Carboxenin Proc.	Adr. Arthr. I		Adr. Arthr. II			
(Dosage in Mg./Kg. Body Weight)						
3-Phenyl-2[1H]-pyridine	10 = 38	12.5 = 51.3	12.5 = 56.9			
4-Phenyl-2[1H]-pyridone	100 = 54.7	12.5 = 55				

or Example:

12. A composition as claimed in any one of claims 7—11, in which A in the formula represents phenyl, thiazolyl, thiienyl, pyridyl or furyl.

13. A composition as claimed in any one of claims 7—12, in which the compound is 3-phenyl-pyridone-2.

5 14. A composition as claimed in any one of claims 7—12, in which the com-
pound is 4-phenyl-pyridone-2.

15. A composition as claimed in any one of claims 7—12, in which the compound is 3-(*p*-dimethylaminophenyl)-pyridone-2.

10 16. A composition as claimed in any one of claims 7—12, in which the com-
pound of Formula A or B has been prepared by a method substantially as set forth
herein.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1971.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

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PATENT SPECIFICATION

(11) 1238959

1238959

NO DRAWINGS

- (21) Application No. 55816/68 (22) Filed 25 Nov. 1968
 (31) Convention Application No. 687.101 (32) Filed 1 Dec. 1967 in
 (33) United States of America (US)
 (45) Complete Specification published 14 July 1971
 (51) International Classification A 61 k 27/00
 (52) Index at acceptance

ASB 381 38Y 401 40Y 410 411 41Y 440 44Y 451 453
 45Y 462 463 46Y 471 472 47Y 480 482 483
 484 485 48Y 490 492 493 49Y 500 502 503 504
 505 50Y 510 511 513 51Y 522 526 52Y 531
 533 53Y 540 541 543 546 54Y 550 55Y 565 566
 56Y 576 57Y 586 58Y 616 61Y 640 641 64Y
 650 651 652 65X 65Y 660 661 663 664 666 667
 66Y 670 67Y
 C2C 173—197—288 17X—27X—287 1E4K4 1E6K4
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 250 25.1 25Y 30Y 313 31Y 321 322 323 326
 328 32Y 332 334 337 338 340 341 342 34Y 351
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 62X 62Y 650 656 660 661 666 670 671 672 680
 681 682 699 69Y 708 720 72X 72Y 73Y 758
 761 762 790 79Y B4A2 B4B B4C B4E KA KD
 KS LF LK MD MG ML MM NR RM RV SF

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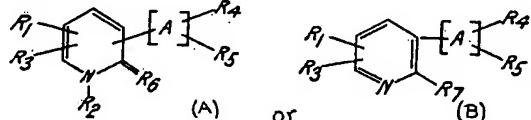
(54) ANTIINFLAMMATORY METHOD AND COMPOSITIONS

(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the treatment of inflammation.

This invention provides a method of treating inflammation in non-human animals which comprises the administration to the animal of from 0.5 to 30 mg/kg of body weight/day of a compound having the formula:

10



5

10

in which

R₁ is hydrogen, alkyl, phenyl, aralkyl, halogen, haloalkyl, alkoxy, amino, dialkylamino, dialkylaminoalkyl, nitro, alkylsulfonyl, phenylsulfonyl, phenoxy, sulfo or triphenylmethyl;

[Price 25p]

phenyl-2-[1H]-pyridinone. A (3 or 4)-amino-2-(*H*)-benzene compound can be diazotized in the presence of a benzene to get Compound VII, directly, nitro benzenes can be heated with pyridines at very elevated temperatures to produce (3 or 4)-phenylpyridines. An open chain substituent on a benzene compound can be cyclized to form the pyridone

R_1 is hydrocarbon, alkyl, alkenyl, phenyl, hydroxyl, amino, alkyl, phenyl, substituted phenyl, quinonyl, alkyl, alkenyl, benzamido, C_6 -alkoxybenzamido, benzylidenebenzamido, phenylureido, amide, benzoxycarbonyl, alkylbenzene, alkyl, dialkylbenzenealkyl, C_6 -alkyl, carboxyalkyl, hydroxylalkyl, cyanooalkyl; R_2 is hydrocarbon or alkyl; R_3 is oxygen or sulfur; R_4 is phenylsulfonyl; R_5 is alkyl, carboxy, amino, dialkylamine, nitro, cyano, sulfamoyl, alkylsulfonamoyl, carboxy, dialkylsulfonamoyl, mercapto, alkylthio, alkylsulfanyl, alkylsulfonanyl, carb-

ring or a piperidone ring which can be oxidized as described above to the 3- or 4-phenyl-2[1H]-pyridone. A (3 or 4)-phenylpyridine 2-sulfonic acid, upon fusion with caustic, gives a 3- or 4-phenyl-2[1H]-pyridone. An alpha pyrone can be treated with ammonia to give a 3- or 4-phenyl-2[1H]-pyridone. 3- or 4-phenylpyridines can be hydroxylated directly in the vapor phase. 3- or 4-phenyl 2-aminopyridines can be diazotized and the diazo compound hydrolysed to give a 3- or 4-phenyl-2[1H]-pyridone. The N-oxides (Compound IV) can be rearranged under the influence of light to give the 3-phenyl-2-[1H]-pyridones. The 1-substituted-3- or 4-phenyl-2[1H]-pyridones (Compound IX) can be prepared by the direct oxidation of the corresponding 3- or 4-phenyl N-pyridinium compounds. These various preparations generally are not as practical in the synthesis of these compounds as the ones described in the Flow Sheet, being either highly selective and applicable to only a few compounds, giving poorer yields or having other inherent weaknesses.

In the treatment of inflammation by 3-phenyl-2[1H]-pyridones, the medicament may be administered orally, intravenously or applied topically. The invention provides pharmaceutical compositions comprising a compound of formula A or B above together with a solid inert diluent, carrier or coating, a flavoured liquid carrier or diluent, or an isotonic injectable liquid carrier or diluent. Also in accordance with the present invention, compounds of formula A or B made by the processes of the present invention are incorporated in pharmaceutical or veterinary compositions that also comprise an inert diluent, carrier or coating. In formulations, it can be pressed into shaped dosage forms, such as pills or tablets, or be encapsulated or dissolved in isotonic solution for I.V. use or made into ointments for topical use. The standard pharmaceutical ingredients normally used in such pharmaceutical formulations can be used in formulating these compounds. Inflammation is treated by the administration of from 0.5 to 30 milligrams of the compound per kg body weight per day. An example of the above class is the simple unsubstituted 3-phenyl-2[1H]-pyridone which should be administered in a dosage range of from 2 to 15 mg/kg of body weight/day. The 3-phenyl-2[1H]-pyridone is effective at 10—30 milligrams per kilogram in rats. The compositions of the present invention may be applied to either animal or human patients since all warm-blooded species are subject to the ills of inflammation.

1. Addition of or to amyl nitrite can be replaced by either organic-solvent-soluble nitrosating agents.

2. Oxidation in an inert solvent, preferably H_2O_2 .

3. Amyl nitrite can be replaced by other organic-solvents, preferably acetic acid.

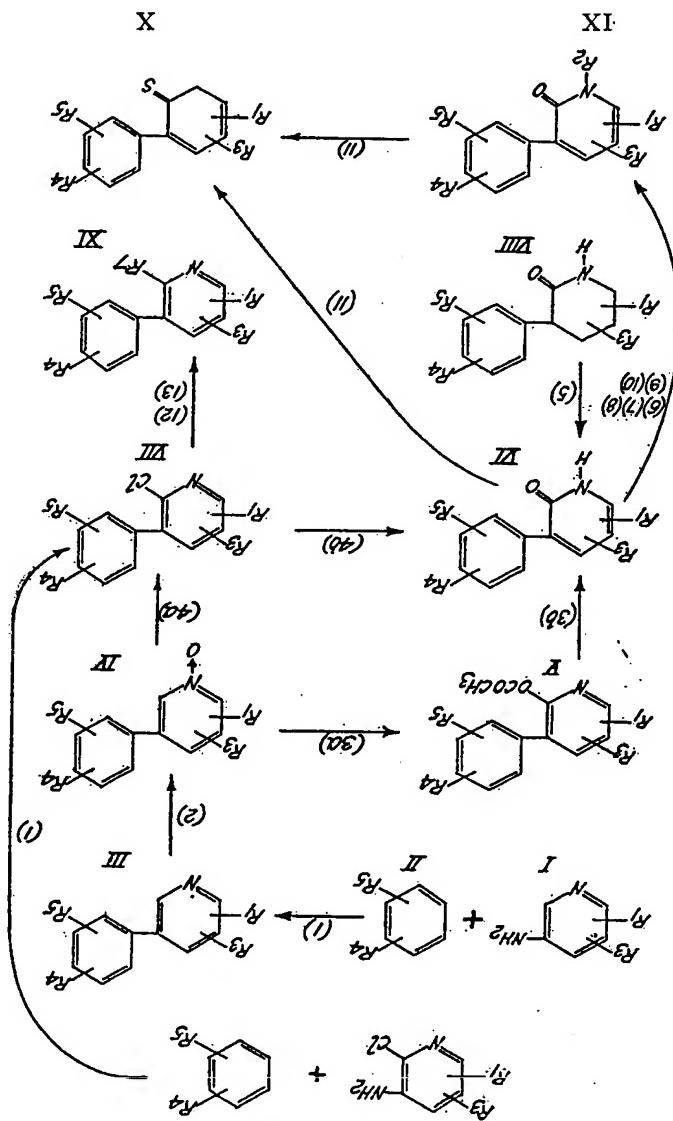
4. (a) Heating with a chlorinating agent, such as PCl_5 , in an inert solvent.
 (b) Hydrolysis, usually by contact with water, also in presence of alkali or acid.

5. Heating with a dehydrating agent such as palladium in an inert atmosphere.

6. Reaction with a strong base, e.g., NaH in an inert atmosphere, followed by addition of an alkylating agent such as an aliphatic tosylate, sulfide or aliphatic thialide.

7. Heating with a strong base (e.g., $NaOH$) and an unsaturated organic compound such as acrylic nitrite or an α -haloacid derivative such as chloroacetic acid. (The latter procedure is described in J. Am. Chem. Soc. 71, 1949, p. 390.)

FLOW-SHEET



8. Reaction with a strong base such as NaH in an inert atmosphere, followed by heating with iodobenzene or a substituted iodobenzene.
 9. Stirring at low temperatures, preferably cold with an N-halo amino compound.
 10. Heating with an alkanoic acid anhydride, preferably with acetic anhydride at 130—140°C.
 11. Heating with P₂S₅ (in the absence of OH, ketone or amino groups in the molecule).
 12. Heating with a metal alkoxide or other alcoholate.
 13. Heating with a metal mercaptide.

10 The preparation of compounds used in the method and compositions of this invention is illustrated by the following Examples 1—34 and some test results are set forth in Example 35.

EXAMPLE 1

15 A. 3-Aminopyridine (39 g.) in 1.5 l. of anhydrous benzene is treated with amyl nitrite (68 g.) and the resulting mixture heated slowly to 81°C., and kept overnight at this temperature. The solution is decanted from some tar which has precipitated, and the excess benzene removed *in vacuo*. Distillation of the residue yields 3-phenylpyridine (38 g.; 59%), b.p. 102—105.5° (2.5 mm.) as a yellow oil.

20 Similarly, when 4-amino pyridine is used in the above example in place of 3-amino pyridine, there is obtained 4-phenylpyridine.

B. Similarly, when the benzene in Part 1A is replaced by toluene, anisole, benzonitrile, nitrobenzene, fluorobenzene, benzotrifluoride, naphthalene, *o*-, *m*-, and *p*-xylenes, *o*-, *m*- and *p*-dichlorobenzenes, hydroquinone dimethyl ether, veratrole, resorcinol dimethyl ether, biphenyl, thiophene, furan or thiazole, the corresponding substituted phenylpyridines, 3-(*o*-, *m*-, and *p*-methylphenyl)-pyridines, 3-(*o*-, *m*-, and *p*-methoxyphenyl)-pyridines, 3-(*o*-, *m*-, and *p*-cyanophenyl)-pyridines, 3-(*o*-, *m*- and *p*-nitrophenyl)-pyridines, 3-(*o*-, *m*- and *p*-fluorophenyl)-pyridines, 3-(*o*-, *m*-, and *p*-trifluoromethylphenyl)-pyridines, 3-(α - and β -naphthyl)-pyridines, 3-(*o,m*-, *m,p*, *o,o'*-*o,p*, *m,m'* and *o,m'* dimethylphenyl)-pyridines, 3-(*o,m*-, *m,p*, *o,o'*-, *o,p*, *m,m'* and *o,m'*-dichlorophenyl)-pyridines, 3-(*o,m*-, *m,p*, *o,o'*-, *o,p*, *m,m'* and *o,m'*-dimethoxyphenyl)-pyridines, 3-(*o*-, *m*-, and *p*-biphenyl)-pyridines, 3-(2-thienyl)-pyridines, 3-(2'- and 3'-furyl)-pyridines, and 3-(2', 4' and 5'-thiazolyl)-pyridines are obtained after separation of isomers via fractional distillation and/or column and vapor-phase chromatography.

C. 3-Aminopyridine (39 g.) in 1.5 l. of anhydrous chlorobenzene is treated with amyl nitrite (68 g.) as described in (A) above. Distillation of the concentrated reaction mixture yields 35.4 g. of the three isomers, b.p. 110—130° at ca. 2.5 mm. The fraction boiling 110—113°C. at ca. 2.5 mm. consists of 11.5 g. of nearly one component material; I.R., N.M.R., U.V. and T.L.C. on this and on products derived from this indicate the *o*-isomer. The other isomers are isolated from the higher boiling fractions via purification of their picrates, followed by regeneration of the free bases. When 4-aminopyridine is used in place of 3-aminopyridine in the above procedure, the corresponding 4-phenylpyridines are obtained.

D. In cases where the benzene-substitute is a solid, an inert co-solvent is used and the amount of benzene-substitute reduced. Also, the phenylpyridines listed in (A) above are obtained by coupling a substituted aniline, as *o*-chloroaniline, with pyridine via the above procedure, and separating the isomeric α -, β - and γ -pyridines, to give the desired 3-(substituted phenyl)-pyridine.

E. When 5-amino-2-picoline is used in place of 3-aminopyridine in procedure (A) above, 6-methyl-3-phenyl)-pyridine is obtained. Similarly, when 5-amino-3-picoline, 3-amino-4-picoline, 5-amino-2-chloropyridine, 3-amino-5-chloropyridine, 3-amino-4-chloropyridine, 5-amino-2-methoxypyridine, 3-amino-5-methoxypyridine, 3-amino-4-methoxypyridine, 5-amino-2-nitropyridine, 3-amino-5-nitropyridine, 3-amino-4-nitropyridine, 5-amino-2-ethoxypyridine, 3-amino-5-ethoxypyridine, 3-amino-4-ethoxypyridine, 5-amino-2-ethylpyridine, 3-amino-4-ethylpyridine, 5-amino-2-phenethylpyridine, 3-amino-4-phenethylpyridine, 5-amino-2-fluoropyridine, 5-amino-2-(methylsulfonyl)-pyridine, 3-amino-4-(methylsulfonyl)-pyridine, 5-amino-2-(phenylsulfonyl)-pyridine, 5-amino-3-chloro-2-phenoxy-pyridine, 5-amino-2-methoxy-4-picoline, and 3-amino-5-phenyl-4-picoline are used in place of 3-aminopyridine in the same procedure, 5-methyl-3-phenylpyridine, 4-methyl-3-phenylpyridine, 6-chloro-3-phenylpyridine, 5-chloro-3-phenylpyridine, 4-chloro-3-phenylpyridine, 6-methoxy-3-phenylpyridine, 5-methoxy-3-phenylpyridine, 4-methoxy-3-phenylpyridine, 6-nitro-3-phenylpyridine, 5-nitro-3-phenylpyridine, 4-nitro-3-phenylpyridine, 6-ethoxy-3-phenyl-

pure solid. Recrystallization from dimethylsulfoxide followed by recrystallization from chloroform and treatment with decolorizing charcoal yields white crystals, m.p. 225—227°C., of 3-phenyl-2[1H]-pyridone.

B. 3-(*o*-Chlorophenyl)-pyridine-*N*-oxide (4.1 g.) and acetic anhydride (10 ml.) are heated, under nitrogen, in an oil bath to 146±2° (bath temperature) and maintained on this temperature for *ca.* eleven hours. On cooling, the mixture is added to a stirred ice-water mixture (80 ml.), and the resultant oil taken up in chloroform. The chloroform is removed *in vacuo*, the residue dissolved in 60 ml. methanol, 7 ml. water and 2 ml. saturated aqueous sodium bicarbonate added, the mixture refluxed *ca.* 15 minutes, the mixture made neutral with 2.5 N hydrochloric acid, the solvents removed, and the residue partitioned between chloroform-water. The chloroform layer is dried, stripped of solvent, and the residue recrystallized from benzene to yield 635 mg. white 3-(*o*-chlorophenyl)-2-[1H]-pyridone, m.p. 203.5—207°.

C. Alternately, the acetic anhydride may be stripped *in vacuo* directly and the methanol-bicarbonate treatment used immediately.

D. When the substituted pyridine oxides from Example 2 are used in place of 3-(*o*-chlorophenyl)-pyridine oxide in the above reaction, the corresponding 2[1H]-pyridones:

3-(*o*-, *m*- and *p*-methylphenyl)-2[1H]-pyridones,

3-(*m*- and *p*-chlorophenyl)-2[1H]-pyridones,

3-(*o*-, *m*- and *p*-methoxyphenyl)-2[1H]-pyridones,

3-(*o*-, *m*- and *p*-cyanophenyl)-2[1H]-pyridones

3-(*o*-, *m*- and *p*-nitrophenyl)-2[1H]-pyridones,

3-(*o*-, *m*- and *p*-fluorophenyl)-2[1H]-pyridones,

3-(*o*-, *m*- and *p*-trifluoromethylphenyl)-2[1H]-pyridones,

3- α - and β -naphthyl-2[1H]-pyridones,

3-(*o*,*m*-dimethylphenyl)-2[1H]-pyridone,

3-(*m*,*p*-dimethylphenyl)-2[1H]-pyridone,

3-(*o*,*o*'-dimethylphenyl)-2[1H]-pyridone,

3-*o*,*p*-dimethylphenyl)-2[1H]-pyridone,

3-(*m*,*m*'-dimethylphenyl)-2[1H]-pyridone,

3-(*o*,*m*'-dimethylphenyl)-2[1H]-pyridone,

the corresponding dichloro and dimethoxy phenyl pyridones,

3-(*o*-, *m*- and *p*-biphenylyl)-2[1H]-pyridones,

3-(2'-thienyl)-2[1H]-pyridone,

3-(2'-furyl)-2[1H]-pyridone,

3-(3'-furyl)-2[1H]-pyridone,

3-(2'-thiazolyl)-2[1H]-pyridone,

3-(4'-thiazolyl)-2[1H]-pyridone,

3-(5'-thiazolyl)-2[1H]-pyridone,

6-methyl-3-phenyl-2[1H]-pyridone,

5-methyl-3-phenyl-2[1H]-pyridone,

4-methyl-3-phenyl-2[1H]-pyridone,

6,5- and 4-chloro-3-phenyl-2[1H]-pyridones,

6,5- and 4-methoxy-3-phenyl-2[1H]-pyridones,

6,5- and 4-nitro-3-phenyl-2[1H]-pyridones,

6,5- and 4-ethoxy-3-phenyl-2[1H]-pyridones,

6- and 4-ethyl-3-phenyl-2[1H]-pyridones,

6- and 4-pheneryl-3-phenyl-2[1H]-pyridones,

6-fluoro-3-phenyl-2[1H]-pyridone,

6- and 4-methylsulfonyl-3-phenyl-2[1H]-pyridones,

6-phenylsulfonyl-3-phenyl-2[1H]-pyridone,

5-chloro-6-phenoxy-3-phenyl-2[1H]-pyridone,

6-methoxy-4-methyl-3-phenyl-2[1H]-pyridone,

4-methyl-3,5-diphenyl-2[1H]-pyridone,

and the corresponding 3-substituted-phenyl derivatives of the above compounds are obtained.

E. In the above cases, the inductive effects of the substituents on the phenyl and pyridine rings help determine the course of the rearrangement, and in some cases of the corresponding 5-phenyl-2[1H]-pyridones are obtained. The isomers are separated by recrystallization and column chromatography techniques.

EXAMPLE 4

A. 2-Methyl-5-phenylpyridine-*N*-oxide (1 g.) phosphorus pentachloride (1.2 g.) and dry chloroform (10 ml.) are refluxed on the water-bath for 1 hour. Ice is added to

EXAMPLE 8

A. *Sodium 3-phenyl-pyridone*

To a suspension of 0.87 gram of 50% NaH (0.018 m.) in 100 mls. of dry benzene is added 3.08 grams (0.018 m.) of 3-phenyl-2[1H]-pyridone. The reaction mixture is heated at 35°C. for 6 hours and allowed to stir at room temperature overnight. The benzene was then evaporated *in vacuo* leaving a residue of sodium 3-phenyl-pyridone.

B. *1,3-Diphenyl-2[1H]-pyridone*

The sodium 3-phenyl-pyridone from above (0.018 m.), 6.04 grams of iodo benzene (0.032 m.) and 0.19 grams of copper (0.003 m.) are mixed with mechanical stirring and heated at 155° under nitrogen for six hours. The reaction mixture is allowed to cool to room temperature overnight and the mixture then extracted well with chloroform. The chloroform extracts are washed with water, dried over sodium sulfate and concentrated. Chromatography of the residue on 500 grams of silica gel and elution with ether-petroleum ether (0—75%) gives 1,3-diphenyl-2[1H]-pyridone.

C. Similarly, when substituted iodo benzenes, e.g. 2-iodonitrobenzene, 3-iodonitrobenzene and 4-iodonitrobenzene, are used in place of iodo benzene in the above example, the corresponding 1-(substituted aryl)-3-phenyl-2[1H]-pyridones are obtained.

EXAMPLE 9

3-Phenyl-1-(2'-quinolyl)-2[1H]-pyridone

A. *2-Bromo-3-phenyl-pyridine*

A mixture of 0.1 moles of 3-phenyl-2[1H]-pyridone and 0.15 moles of phosphorus tribromide are heated for 3 hours at 180°. The reaction mixture is cooled, decomposed in ice water, made alkaline with sodium hydroxide and extracted well with ether. The combined ethereal extracts are dried over sodium sulfate and concentrated *in vacuo* to yield 2-bromo-3-phenyl-pyridine.

B. *3-Phenyl-1(2'-quinolyl)-2[1H]-pyridone*

A mixture of 0.02 mole of quinoline-N-oxide and 0.022 mole of 2-bromo-3-phenyl-pyridine is heated on the steam bath for 8 hours. The reaction mixture is cooled, taken up in water containing a little hydrochloric acid and washed with ether. The aqueous layer is made alkaline with potassium carbonate solution and extracted well with chloroform. The combined chloroform extracts are dried over potassium carbonate and concentrated to yield 3-phenyl-1-(2'-quinolyl)-2[1H]-pyridone.

C. Similarly, when 2-picoline-N-oxide, 3-picoline-N-oxide or 4-picoline-N-oxide is used in place of quinoline-N-oxide in the above procedure, there is obtained 3-phenyl-1-[2'-(6'-methylpyridyl)]-2[1H]-pyridone, 3-phenyl-1-[2'-(5'-methylpyridyl)]-2[1H]-pyridone, and 3-phenyl-1-[2'-(4'-methylpyridyl)]-2[1H]-pyridone.

EXAMPLE 10

A solution of chloramine is prepared by treating at 0°C. 65 ml. of a 1.93 m. neutral sodium hypochlorite solution (0.125 m.) with 20 mls. of 1.84 m. NH₂OH (0.375 m.). The above mixture is allowed to stand for one hour in an ice-salt bath and then 0.125 m. of sodium 3-phenyl-pyridone is added. The reaction mixture is stirred overnight at 0—10°C. and is then continuously extracted with ether for 24 hours. The ethereal extracts are dried over sodium sulfate and concentrated to yield 1-amino-3-phenyl-2[1H]-pyridone.

EXAMPLE 11

1-Hydroxy-3-phenyl-2[1H]-pyridone

A. *2-Chloro-3-phenyl-pyridine-N-oxide*

0.2 mole of 2-chloro-3-phenyl-pyridine is treated with 25 mls. of glacial acetic acid and 22 mls. of 40% peracetic acid. The temperature of the reaction mixture is kept at 70°C. for 3 hours. The reaction mixture is concentrated and extracted with chloroform and the chloroform extracts are concentrated to yield 2-chloro-3-phenyl-pyridine-N-oxide.

B. 0.01 mole of 2-chloro-3-phenyl-pyridine-N-oxide and 20 mls. of acetic anhydride are heated for 3 hours at 130—140°. The reaction mixture is then concentrated *in vacuo* to yield crude 1-hydroxy-3-phenyl-2[1H]-pyridone.

EXAMPLE 12

A. A mixture of 0.02 mole of 3-phenyl-2[1H]-pyridone and 0.025 mole of phosphorus pentasulfide is heated for 6 hours at 160°C. The reaction mixture is then

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dispersed into 100 ml. of hot water, cooled and the 3-phenyl-2-[H]-thiopyrididine collected by filtration. Chromatography on 400 gm. of silica gel and elution with ether-
acetone (0—90%) gives 3-phenyl-2-[H]-thiopyrididine. M.p. 229—237°.

EXAMPLE 13

powdered into 100 ml. of hot water, cooled and the 3-phenyl-2-[H]-thiopryridine col-lected by filtration. Chromatography on 400 gm. of silica gel and elution with ether-receted by filtration. Chromatography on 400 gm. of silica gel and elution with ether-
performed on 90% gives 3-phenyl-2-[H]-thiopryridine. M.p. 229–237°.

dispersed into 100 ml. of hot water, cooled and the 3-phenyl-2-[H]-thiopyrididine collected by filtration. Chromatography on 400 gm. of silica gel and elution with ether-
acetone (0—90%) gives 3-phenyl-2-[H]-thiopyrididine. M.p. 229—237°.

hours. A piece of sodium methoxide, such as in the above example, the corresponds alkoxides of carboxylic acids are added to dry DMF to 0.01 moles of NaH in 30 cc. dry DMF, and stirring 1

25 hour.
26 alcohols in 20 cc. dry DMF to 0.01 moles of NaH in 30 cc. dry DMF, and stirring 1
27 phenylpyridines are obtained. The alkoxides are prepared by adding 0.01 mole of the
28 in place of sodium methoxide, such as in the above example, the corresponding alkox-
29 acids, methylbenzoate, propionate, etc., to the reaction mixture.

of the methyl mercaptoide, the corresponding 2-sulfide is obtained.

of the methyl mercaptide, the corresponding 2-sulfide is obtained.

A mixture of 0.01 mole of 1-(2-cyanoethyl)-3-phenyl-2[1H]-pyridone, 50 ml. of acetic acid and 50 ml. of 10% sulfuric acid is refluxed for 4 hours. The reaction mixture is then concentrated, poured into water and extracted well with chloroform. The combined chloroform extracts are dried over sodium sulfate and concentrated to give 1-(2-carboxyethyl)-3-phenyl-2[1H]-pyridone.

EXAMPLE 15 A mixture of 0.01 mole of 1-(2-*cyanoethyl*)-3-phenyl-2-[1H]-pyridone, 50 ml. of acetic acid and 50 ml. of 10% sulfuric acid is refluxed for 4 hours. The reaction mixture is then concentrated, poured into water and extracted well with chloroform. The combined chloroform extracts are dried over sodium sulfate and concentrated to give 1-(2-carboxyethyl)-3-phenyl-2-[1H]-pyridone.

A mixture of 0.01 mole of 1-(*o*-hydroxyethyl)-3-phenyl-2-[¹H]-pyridone and 25 cc. of concentrated hydrochloric acid is heated in a sealed tube for 60 hours at 120°. The reaction mixture is cooled and then concentrated in vacuo to yield 1-(*o*-chloroethyl)-3-phenyl-2-[¹H]-pyridone.

A mixture of 0.01 mole of 1-(2-hydroxyethyl)-3-phenyl-2-[1H]-pyridine and 25 cc. of concentrated hydrochloric acid is heated in a sealed tube for 60 hours at 120°. The reaction mixture is cooled and then concentrated in *vacuo* to yield 1-(2-chloro-ethyl)-3-phenyl-2-[1H]-pyridine.

groups after preparation of the phenyl pyridone nucleus.

groups after preparation of the phenyl pyridone nucleus.

tion from benzene (concentrating to *ca.* 40 ml. hot) yields 8.15 mg. very pale pink cotton-like crystals, m.p. 157.5—159°, of 5-chloro-3-phenyl-2[1H]-pyridone.

EXAMPLE 18

5-Dimethylamino-3-phenyl-2[1H]-pyridone

5-Chloro-3-phenyl-2[1H]-pyridone (1 g.) in anhydrous dimethylformamide (50 ml.) is saturated with dimethylamine, and the resultant mixture heated in a lined stainless-steel bomb for several hours. The solvent is removed *in vacuo*, the residue distributed between chloroform and water, the chloroform layer dried, solvent stripped, and the residue chromatographed on a silica gel column using a methanol-methylene chloride eluent ('/v0—100% MeOH) to yield the title compound.

EXAMPLE 19

3-*p*-Hydroxyphenyl-2[1H]-pyridone

3-(*p*-Methoxyphenyl)-2[1H]-pyridone (2 g.) is added to a stirred 10-g. portion of pyridine hydrochloride at 188°. A dry nitrogen atmosphere is maintained. The mixture is kept 20 minutes, allowed to cool, then added to 45 g. of ice. The crude product is collected, dried and recrystallized to yield the title compound.

Similarly, when the *o*- and *m*-methoxyphenylpyridones are substituted for the *p*-isomer in the above reaction, the corresponding *o*- and *m*-hydroxy analogs are obtained.

EXAMPLE 20

3-(*p*-Aminophenyl)-2[1H]-pyridone

3-(*p*-Nitrophenyl)-2[1H]-pyridone (1 g.) in warm dioxane (50 ml.) is reduced under a hydrogen atmosphere in the presence of 0.3 g. 5% Pd/C. The mixture is filtered, the cake washed well with warm dioxane, the combined filtrates concentrated to residue, the residue recrystallized to yield title compound.

Alternatively, when the dioxane solution is treated with anhydrous ethereal-hydrogen chloride solution, the hydrochloride precipitates. When the corresponding *o*- and *m*-nitrophenyl-pyridones are used in the above reduction the *o*- and *m*-amino-phenyl-pyridones are obtained.

EXAMPLE 21

3-(*p*-Dimethylaminophenyl)-2[1H]-pyridone

3-(*p*-Nitrophenyl)-2[1H]-pyridone (1 g.) in methanol (100 ml.) containing glacial acetic acid (1 ml.) and 37% formaldehyde solution (3 ml.) is reduced in the presence of Raney nickel (1/4 tsp.) under a hydrogen atmosphere. The mixture is filtered, the cake washed with methanol, and the combined filtrates concentrated to a residue. Chromatography on an alumina column using a system comprising methanol and methylene chloride ('/v0—100%) yields the title compound.

When the *o*- and *m*-nitro isomers are used in place of the *p*-isomer in the above reduction, the corresponding *o*- and *m*-dimethylaminophenyl-2-pyridones are obtained.

EXAMPLE 22

3-(*p*-Carbamoylphenyl)-2[1H]-pyridone

3-(*p*-Cyanophenyl)-2[1H]-pyridone (5 g.) is added to a stirred ice-cold portion of concentrated sulfuric acid (20 g.) and the mixture stirred overnight, added to ice-water, the crude product collected, dried and recrystallized to yield the title compound. When the *o*- and *m*-cyanophenylpyridones are used in the above reaction, the corresponding *o*- and *m*-carbamoylphenyl isomers are obtained.

EXAMPLE 23

3-(*p*-Carboxyphenyl)-2[1H]-pyridone

3-(*p*-Cyanophenyl)-2[1H]-pyridone (1 g.) in 30 ml. of a 1:1 mixture of glacial acetic acid and 20% hydrochloric acid is heated for twelve hours, the solvent removed *in vacuo*, the residue partitioned between chloroform and nearly saturated sodium bicarbonate solution, the bicarbonate solution filtered and acidified, the precipitate collected, dried and recrystallized to yield the title compound.

When the *o*- and *m*-cyanophenyl-pyridones are used in the above reaction, the corresponding *o*- and *m*-carboxyphenyl isomers are obtained.

EXAMPLE 24

(1-Methyl-3-phenyl-2[1H]-pyridone-5-sulfonic acid

When 1-methyl-3-phenyl-2[1H]-pyridone is treated with chlorosulfonic acid according to the procedure of German Patent 601,896, there is obtained 1-methyl-3-phenyl-2[1H]-pyridone-5-sulfonic acid.

EXAMPLE 25
3-Phenyl-5-triphenylmethyl-2-[1H]-pyridone
and recrystallized to give the title compound.
3-Phenyl-2-[1H]-pyridone (3 g.) and triethyl chloride (3 g.) are intimately mixed
and heated at ca. 250° in a metal-bath for 30 minutes, the reaction mixture cooled,
and 60 ml. of boiling ethanol added, the solid filtered, washed with fresh ethanol,

EXAMPLE 26
5-Amino-3-phenyl-2-[1H]-pyridone
When 5-nitro-3-phenyl-2-[1H]-pyridone is reduced under the conditions described
in Example 20 above, the title compound is obtained.
When the 4- and 6-nitro isomers are used in place of the 5-nitro compound,
the corresponding 4- and 6-amino-3-phenyl-2-[1H]-pyridones are obtained.

EXAMPLE 27
5-Methyl-3-phenyl-2-[1H]-pyridone
5-Dimethylaminomethyl-3-phenyl-2-[1H]-pyridone
In carbon tetrachloride (250 ml.) are reduced under irradiation for ca. 15 mins. (Oca-
sionally a trace of benzoyl peroxide is necessary to initiate reaction), cooled, filtered,
and the filtrate concentrated in vacuo to a residue.
The residue is taken up in ethanol, the solvent removed in vacuo, and the residue chromatographed on
an alumina column using a methanol-methylene chloride system (v/v 0—100%). As
sealed and heated, the solvent removed in vacuo, and the residue chromatographed on
an alumina column using a methanol-methylene chloride system (v/v 0—100%).
Similarly, when the 4- and 6-methyl isomers are used in the above
process, the corresponding 4- and 6-dimethylaminomethyl isomers are obtained.

EXAMPLE 28
3-(p-Mercaptophenyl)-2-[1H]-pyridone
The title compound is prepared from 3-(p-aminophenyl)-2-[1H]-pyridone by the
procedure of Taber & Fukushima for thiocresol (Org. Syn., Coll. Vol. III, p. 809).
but using chloroform as the organic extracrant, omitting the 10% sodium hydroxide
wash, and hydrolyzing the intermediate thiocresonate under milder conditions. The
mixture is then acidified, the solvent removed in vacuo, and the residue recrystallized,
using deoxygenated solvents to avoid disulfide formation.
Similarly, when the o- and m-aminophenyl isomers are used in place of the p-isomer in
the above reaction, the corresponding o- and m-mercapto isomers are obtained.
The procedure used by Wallace (Tetrahedron Letters (1963) 1131) for benzene
sulfonic acid is used.

EXAMPLE 30
p-(2-[1H]-Pyridon-3-yl)-benzenesulfonic acid
3-(p-Mercaptophenyl)-2-[1H]-pyridone is stirred at room temperature in dimethyl sulfoxide
p-[2-[1H]-Pyridon-3-yl]-benzenesulfonic acid (0.005 M) is added to thionyl chlor-
ide (50 ml.), containing one drop of dimethylformamide. The mixture is stirred over-
night at room temperature, the excess of thionyl chloride removed in vacuo, dry ben-
zene added, removed in vacuo, and the residue pumped out to remove all traces of
thionyl chloride. The acid chloride is then taken up in anhydrous ether and added to
an aqueous solution containing two equivalents of ammonia, stirred for several hours,
the product collected, dried, and treated as in Example 4B above to hydrolyze any 2-
chloro derivative present. Recrystallization yields *p*-(2-[1H]-Pyridon-3-yl)-benzenesulf-
onic acid.

EXAMPLE 31
When the o- and m-sulfonic acid isomers are used in the above reaction, the cor-
responding o- and m-sulfonic acid isomers are obtained.
When methylamine, dimethylamine or sulfide is used in place of ammonia in
the above reaction, the corresponding N-substituted sulfonamides are obtained.

EXAMPLE 32
3-Phenyl-5-triphenylmethyl-2-[1H]-pyridone
and 60 ml. of boiling ethanol added, the solid filtered, washed with fresh ethanol,
and heated at ca. 250° in a metal-bath for 30 minutes, the reaction mixture cooled,
and recrystallized to give the title compound.

EXAMPLE 33
3-Phenyl-2-[1H]-pyridone (3 g.) and triethyl chloride (3 g.) are intimately mixed
and heated at ca. 250° in a metal-bath for 30 minutes, the reaction mixture cooled,
and recrystallized to give the title compound.

EXAMPLE 31**2-Acetoxy-3-phenyl-pyridine**

A mixture of 0.01 mole of 3-phenyl-pyridine-*N*-oxide is refluxed for 12 hours in 50 cc. of acetic anhydride. Concentration of the reaction mixture *in vacuo* yields 2-acetoxy-3-phenyl-pyridine.

EXAMPLE 32**1-Benzamido-3-phenyl-2[1H]-pyridone**

A. To a mixture of 0.01 mole of 1-amino-3-phenyl-2-[1H]-pyridone and 5.0 grams of anhydrous potassium carbonate in 100 mls. of chloroform is added portionwise with stirring 0.01 mole of benzoyl chloride. The reaction mixture is stirred for 4 hours at reflux, then cooled and filtered. The filtrate is concentrated *in vacuo* to yield 1-benzamido-3-phenyl-2[1H]-pyridone.

B. When acetyl chloride is used in place of benzoyl chloride in the above example, there is obtained 1-acetamido-3-phenyl-2-[1H]-pyridone.

C. When carbobenzoxy chloride is used in place of benzoyl chloride in the procedure of part (A), 1-carbobenzoxyamino-3-phenyl-2[1H]-pyridone is obtained.

D. When ethyl chloroformate is used in place of benzoyl chloride in the procedure of part (A), 1-carbethoxyamino-3-phenyl-2[1H]-pyridone is obtained.

E. A mixture of 0.01 mole of 1-amino-3-phenyl-2[1H]-pyridone and 0.01 mole of benzaldehyde is refluxed for 3 hours in 30 mls. of ethanol. The reaction mixture is then concentrated to yield 1-benzylidineamino-3-phenyl-2[2H]-pyridone.

F. To 0.01 mole of 1-amino-3-phenyl-2[1H]-pyridone in 100 mls. of anhydrous ether is added 0.01 mole of phenylisocyanate. The reaction mixture is refluxed for one hour, then concentrated to yield 1-(*N'*-phenylureido)-3-phenyl-2[1H]-pyridone.

EXAMPLE 33**3-(*p*-Methylsulfinylphenyl)-2[1H]-pyridone**

3-(*p*-Methylmercaptophenyl)-2[1H]-pyridone (0.001 mole) is stirred in methanol (50 ml.) and sodium metaperiodate (0.001 mole), dissolved in a minimum of water, is added. The mixture is stirred at room temperature for several days and then filtered. The filtrate is concentrated *in vacuo* and partitioned between chloroform and water. The chloroform layer is dried over sodium sulfate and the chloroform is removed *in vacuo*. The residue is recrystallized to yield the above compound.

When the *o*- and *m*-methylmercaptophenyl-pyridones are used in the above process, the corresponding *o*- and *m*-methylsulfinylphenyl-pyridones are obtained.

EXAMPLE 34**3-(*p*-Methylsulfonylphenyl)-2[1H]-pyridone**

To 3-(*p*-Methylmercaptophenyl)-2[1H]-pyridone (1 g.) in glacial acetic acid (25 ml.) is added 30% aqueous hydrogen peroxide (2 ml.), and the resultant mixture is allowed to stir several days at room temperature. A minimum of sodium bisulfite is added to destroy the excess peroxide. The solvent is removed *in vacuo* and the residue is recrystallized to give the above compound.

When the *o*- and *m*-methylmercaptophenyl-pyridones are used in the above process, the corresponding *o*- and *m*-methylsulfonylphenyl-2[1H]-pyridones are obtained.

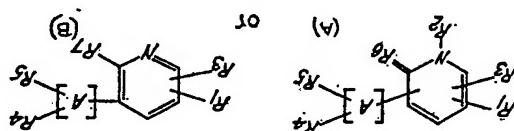
EXAMPLE 35

The testing procedures used are essentially those of 1) Winter, *et al*, Proc. Soc. Exper. Biol. 111 (1962), p. 544 (Carrogeenan-induced Foot Inflammation); 2) Stoerk *et al*, Am. J. Pathol. 30 (1954), p. 616 (Adjuvant Arthritis I); and 3) Newbould, Brit. J. Pharmacol. 24 (1965), p. 632 (Adjuvant Arthritis-II).

or Example:

WHAT WE CLAIM IS: —

1. A method of treating inflammation in non-human animals that comprises administering to the animal from 0.5 to 30 mg/kg body weight/day of a compound having the formula:



Compound	Dose	Inhibition %	Dose	Inhibition %	Dose	Inhibition %
3-Phenyl-2-[1H]-pyridone	10	= 38	12.5	= 51.3	12.5	= 56.9
4-Phenyl-2-[1H]-pyridone	100	= 54.7	12.5	= 55		

Carbogeenin Proc.	Adi. Arthr. I	Adi. Arthr. II
(Dosage in Mg./Kg. Body Weight)		

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the general formula A or B set forth in claim 1, together with an isotonic injectable liquid carrier or diluent.

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10. A pharmaceutical or veterinary composition comprising a compound having the general formula A or B set forth in claim 1, together with a flavored liquid carrier or diluent.

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9. A pharmaceutical or veterinary composition comprising a compound having the general formula A or B set forth in claim 1, in the form of a topically administered tablet or ointment.

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8. A composition as claimed in claim 7, in the form of a pill, tablet or capsule.

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7. A pharmaceutical or veterinary composition comprising a compound having the general formula A or B set forth in claim 11, together with a solid inert diluent, phenyl-pyridone-2.

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6. A method as claimed in claim 3, in which the compound is 4-phenyl-pyridone-2.

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5. A method as claimed in claim 3, in which the compound is 3-phenyl-pyridone-

10

4. A method as claimed in claim 3, in which the compound is 3-phenyl-pyridone-2, phenyl, diazodiy, thienyl, pyridyl or furyl.

5

3. A method as claimed in claim 1, in which A in the formula represents alkynyl, alkynoyl and alkoxo radicals containing not more than five carbon atoms.

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2. A method as claimed in claim 1, in which the administration is oral.

30

1. A method as claimed in claim 1, in which the compound is 3-(p-dimethylaminophenyl)-pyridone-2.

25

phenyl, diazodiy, thienyl, pyridyl or furyl.

15

WHAT WE CLAIM IS: —

Compound	Dose	Inhibition %	Dose	Inhibition %	Dose	Inhibition %
3-Phenyl-2-[1H]-pyridone	10	= 38	12.5	= 51.3	12.5	= 56.9
4-Phenyl-2-[1H]-pyridone	100	= 54.7	12.5	= 55		

12. A composition as claimed in any one of claims 7—11, in which A in the formula represents phenyl, thiazolyl, thiienyl, pyridyl or furyl.
13. A composition as claimed in any one of claims 7—12, in which the compound is 3-phenyl-pyridone-2.
- 5 14. A composition as claimed in any one of claims 7—12, in which the compound is 4-phenyl-pyridone-2.
15. A composition as claimed in any one of claims 7—12, in which the compound is 3-(*p*-dimethylaminophenyl)-pyridone-2.
- 10 16. A composition as claimed in any one of claims 7—12, in which the compound of Formula A or B has been prepared by a method substantially as set forth herein.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1971.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

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